

AMENDMENTS TO THE CLAIMS

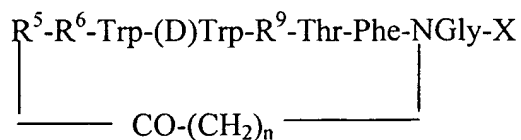
The following listing of claims replaces all prior versions and listings of claims in this application:

1. (Currently Amended) A backbone cyclized analog of somatostatin of three to twenty-four amino acids that incorporates at least one building unit, said building unit containing one nitrogen atom of the peptide backbone connected to a bridging group comprising an amide, thioether, thioester, disulfide, urea, carbamate, or sulfonamide, wherein at least one building unit is connected via the bridging group to form a cyclic structure with a moiety selected from the group consisting of a second building unit, the side chain of an amino acid residue of the sequence or a terminal amino acid residue, further comprising a chelating moiety covalently bound to said backbone cyclized analog and a radioisotope.

2. (Original) The backbone cyclized analog of claim 1 wherein the chelating moiety is selected from a moiety comprising four donor atoms or eight donor atoms.

3. (Currently Amended) The somatostatin analog of claim [[4]] 1 wherein the chelating moiety is selected from 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) and diethylenetriaminepentaacetic acid (DTPA).

4. (Currently Amended) ~~A The somatostatin analog of claim 1 wherein the~~ backbone cyclized somatostatin analog having the general Formula No. 6



Formula No. 6

wherein n is 1 to 5;

X designates a terminal carboxy acid, amide or alcohol group;

R⁵ is 1,3-dicarbonyl-cyclopropane, phthalic acid, maleic acid, glutamic acid, valeric acid, diaminoethane-CO, diaminopropane-CO, or GABA;

R⁶ is Phe or Tyr; and

R⁹ is (L)- or (D)- Lys;

a chelating moiety covalently bound to said backbone cyclized analog; and
a radioisotope.

5. (Original) The backbone cyclized analog of claim 4 selected from the group of:

1,3-dicarbonyl-Cyclopropane*-Trp-Trp-(D)Trp-Lys-Thr-Phe-GlyN₃-NH₂;

Glutamic acid*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyN₃-NH₂;

Diaminoethane*-CO-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC₃-NH₂;

Diaminoethane*-CO-Tyr-Trp-(D)Trp-Lys-Thr-Phe-GlyC₃-NH₂;

Diaminopropan*-CO-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC₃-NH₂;

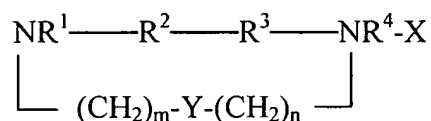
Diaminoethane*-CO-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC₃-NH₂;

GABA*-Phe-Trp-(D)Trp-(D)Lys-Thr-Phe-GlyC₃-NH₂;

GABA*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC₃-NH₂;

wherein the asterisk denotes that the bridging group is connected between the free functional group of that residue and the N^α-ω-functionalized derivative of the Gly residue.

6. (Currently Amended) ~~A The somatostatin analog of claim 1 wherein the~~
backbone cyclized somatostatin analog having the general Formula No. 7



Formula No. 7

wherein m and n are 1 to 5;

X designates a terminal carboxy acid, amide or alcohol group;

R₁ is Trp, (L)- or (D)- Lys, Ala, or Phe;

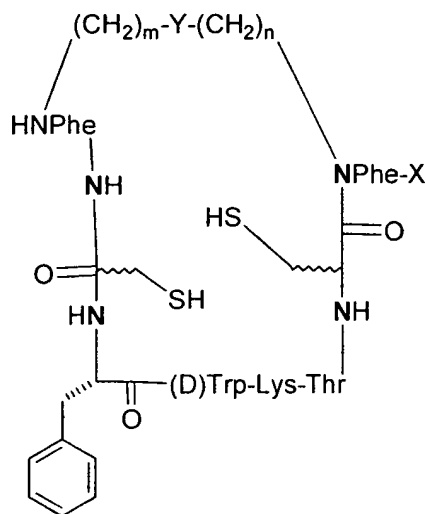
R₂ is Ala, (L)- or (D)- Trp, or Lys;

R₃ is (D)Trp, (L)- or (D)- Phe, Lys, Pro, or (D)Ala;

R₄ is Lys, (D)Phe, (L)- or (D)- Ala, Trp, Gly; and

Y is amide, thioether, thioester, disulfide, urea, carbamate, or sulfonamide;
a chelating moiety covalently bound to said backbone cyclized analog ; and
a radioisotope.

7. (Currently Amended) ~~A The somatostatin analog of claim 1 wherein the~~
backbone cyclized somatostatin analog having the general Formula No. 8



Formula No. 8

wherein m and n are 1 to 5;

X designates a terminal carboxy acid, amide or alcohol group;

Y is amide, thioether, thioester disulfide, urea, carbamate, or sulfonamide; and

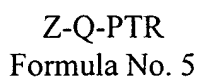
the two cysteine residues are independently L or D;

a chelating moiety covalently bound to said backbone cyclized analog; and

a radioisotope.

8. (Original) The somatostatin analog of claim 1 having the general Formula No.

5:



wherein

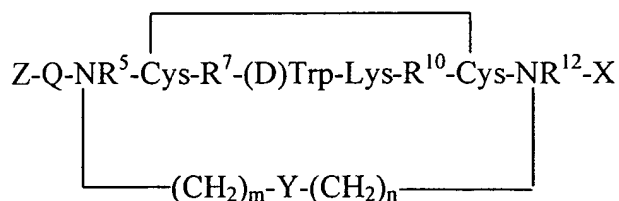
Z is a chelating moiety comprising: (i) four donor atoms selected from the group of N₃S and N₂S₂ that through metal complexation form three five- to six-membered rings or (ii) eight donor atoms that, through metal complexation, form stable five- to six-membered rings;

Q is a direct bond or a linker moiety which can be coupled to a free functional group of the peptide; and PTR denotes a backbone cyclized SST analog according to the present invention.

9. (Original) The somatostatin analog of claim 8 wherein Q is selected from the group of a direct bond, diaminopropionic acid (Dpr), diaminobutyric acid (Dab), gamma aminobutyric acid (GABA), aminohexanoic acid, polyethylene glycol (PEG), 4-aminobutyric acid, 6-aminocaproic acid, and β -alanine, and Z is selected from the group of mercaptoacetyl-Gly-Gly-Gly (MAG3), 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) and diethylenetriaminepentaacetic acid (DTPA).

10. (Original) The somatostatin analog of claim 9 wherein Z is selected from the group of mercaptoacetyl-Gly-Gly-Gly (MAG3), 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) and diethylenetriaminepentaacetic acid (DTPA); and Q is selected from a direct bond and Gly.

11. (Currently Amended) A The somatostatin analog of claim 1 wherein the backbone cyclized somatostatin analog with a chelating moiety covalently bound to said backbone cyclized analog having the general Formula No. 9



Formula No. 9

wherein m and n are 1 to 5;

X designates a terminal carboxy acid, amide or alcohol group;

Q is a direct bond or a linker moiety which can be coupled to any free functional group of the peptide;

Z is a chelating moiety comprising: (i) four donor atoms selected from the group of N₃S and N₂S₂ that through metal complexation form 5- to 6-membered rings or (ii) eight donor atoms that, through metal complexation, form stable five- to six-membered rings;

R⁵ is (D)- or (L)-Phe or (D)- or (L)-Ala;

R⁷ is (D)- or (L)-Trp, (D)- or (L)-Phe, (D)- or (L)- 1Nal, or (D)- or (L)- 2Nal, or (D)- or (L) Tyr;

R¹⁰ is Thr, Gly, Abu, Ser, Cys, Val, (D)- or (L)-Ala, or (D)- or (L)-Phe;

R¹² is (D)- or (L)-Phe or (D)- or (L)-Ala; and

Y is amide, thioether, thioester disulfide, urea, carbamate, or sulfonamide;
and a radioisotope.

12. (Original) The somatostatin analog of claim 11 wherein the backbone cyclized somatostatin analog is selected from the group of:

MAG3-PheC3**-Cys*-Phe-(D)Trp-Lys-Thr-Cys*-PheN3**-NH₂;

MA-Dap(MA)-Gly-Phe(C3**-Cys*-Phe-(D)Trp-Lys-Thr-Cys*-Phe(N3**-NH₂;

MA-Dap(Gly)-Gly-Phe(C3**-Cys*-Phe-(D)Trp-Lys-Thr-Cys*-Phe(N3**-NH₂;

Gly-Dap(MA)-Gly-Phe(C3**-Cys*-Phe-(D)Trp-Lys-Thr-Cys*-Phe(N3**-NH₂;

MA-Dap(MA)-GABA-Phe(C3**-Cys*-Phe-(D)Trp-Lys-Thr-Cys*-Phe(N3**-NH₂;

MA-Dap(Gly)-GABA-Phe(C3**-Cys*-Phe-(D)Trp-Lys-Thr-Cys*-Phe(N3**-NH₂;

Gly-Dap(MA)-GABA-Phe(C3**-Cys*-Phe-(D)Trp-Lys-Thr-Cys*-Phe(N3**-NH₂;

wherein MA denotes mercaptoacetyl, Dpr denotes diaminopropionic acid, Dab denotes diaminobutyric acid, GABA denotes gamma aminobutyric acid, one asterisk denotes that the two cysteines form a disulfide bridge, and two asterisks denotes that a second bridging group is connected between the N^α-ω-functionalized derivative of marked residues.

13. (Currently Amended) A The somatostatin analog of claim 1 wherein the backbone cyclized somatostatin analog with a chelating moiety covalently bound to said backbone cyclized analog having the general Formula No. 10



R⁹ is Lys;
R¹⁰ is Thr;
R¹¹ is Phe;
R¹² is Gly; and
n is 3.

15. (Original) The somatostatin analog of claim 13 wherein the backbone cyclized somatostatin analog is selected from the group of:

In-DTPA-Gly-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
In-DTPA-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
In-DTPA-β-Ala-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
In-DTPA-GABA-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
In-DTPA-5-aminopentanoic acid-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
In-DTPA-3-aminomethylbenzoic acid-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
ReO-MA-Dpr(MA)-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
ReO-MA-Dpr(MA)-Gly-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
ReO-MA-Dpr(MA)-βAla-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
ReO-MA-Dpr(MA)-GABA-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
ReO-MA-Dpr(MA)-5-aminopentanoic acid-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
ReO-MA-Dpr(MA)-6-aminohexanoic acid-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
ReO-MA-Gly-Gly-Gly-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
ReO-MA-Gly-Gly-Gly-Gly-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
ReO-MA-Gly-Gly-Gly-GABA-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
ReO-MA-Gly-Gly-Gly-5-aminopentanoic acid-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;

wherein MA denotes mercaptoacetyl, Dpr denotes diaminopropionic acid, Dab denotes diaminobutyric acid, GABA denotes gamma aminobutyric acid, and the asterisk denotes that the

bridging group is connected between the free functional group of that residue and the N^α-ω-functionalized derivative of the Gly residue.

16. (Cancelled)

17. (Currently Amended) The somatostatin analog according to claim [[16]] 1 wherein the radioisotope is selected from the group consisting of ^{99m}Tc, ¹⁸⁶Re, ¹⁸⁸Re, indium, yttrium, lutetium, gallium and gadolinium.

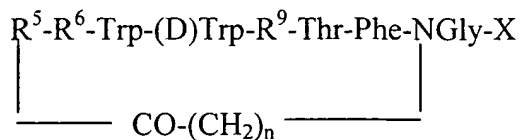
18. (Withdrawn) A method for diagnosing or treating cancer and allograft rejection comprising administering a backbone cyclized analog of somatostatin according to claim 1 optionally with a pharmaceutically acceptable carrier.

19. (Withdrawn) The method according to claim 18 wherein the backbone cyclic analog is used for imaging metastases.

20. (Withdrawn) The method according to claim 18 wherein the backbone cyclic analog is labeled with a detectable tracer.

21. (Withdrawn) The method according to claim 18 wherein the chelating moiety is selected from 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) and diethylenetriaminepentaacetic acid (DTPA).

22. (Withdrawn) The method according to claim 18 wherein the backbone cyclized somatostatin analog having the general Formula No. 6



Formula No. 6

wherein n is 1 to 5;

X designates a terminal carboxy acid, amide or alcohol group;

R⁵ is 1,3-dicarbonyl-cyclopropane, phthalic acid, maleic acid, glutamic acid, valeric acid, diaminoethane-CO, diaminopropane-CO, or GABA;

R⁶ is Phe or Tyr; and

R⁹ is (L)- or (D)- Lys.

23. (Withdrawn) The method according to claim 22 selected from the group of:

1,3-dicarbonyl-cyclopropane*-Tyr-Trp-(D)Trp-Lys-Thr-Phe-GlyN3-NH₂;

Glutamic acid*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyN3-NH₂;

Diaminoethane*-CO-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3-NH₂;

Diaminoethane*-CO-Tyr-Trp-(D)Trp-Lys-Thr-Phe-GlyC3-NH₂;

Diaminopropan*-CO-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3-NH₂;

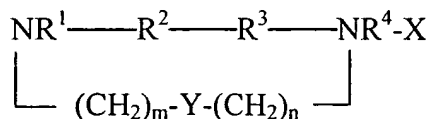
Diaminoethane*-CO-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3-NH₂;

GABA*-Phe-Trp-(D)Trp-(D)Lys-Thr-Phe-GlyC3-NH₂;

GABA*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3-NH₂;

wherein GABA denotes gamma aminobutyric acid, and the asterisk denotes that the bridging group is connected between the free functional group of that residue and the N^α-ω-functionalized derivative of the Gly residue.

24. (Withdrawn) The method according to claim 18 wherein the backbone cyclized somatostatin analog having the general Formula No. 7



Formula No. 7

wherein m and n are 1 to 5;

X designates a terminal carboxy acid, amide or alcohol group;

R1 is Trp, (L)- or (D)- Lys, Ala, or Phe;

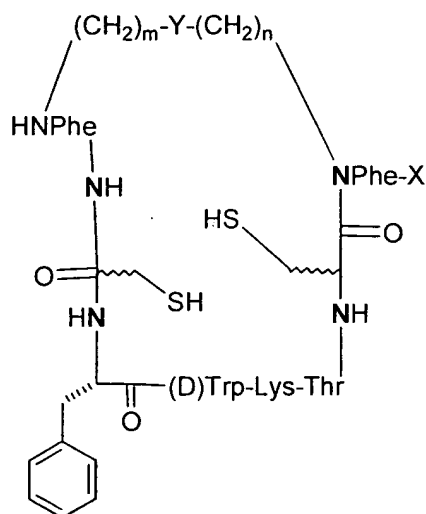
R2 is Ala, (L)- or (D)- Trp, or Lys;

R3 is (D)Trp, (L)- or (D)- Phe, Lys, Pro, or (D)Ala;

R4 is Lys, (D)Phe, (L)- or (D)- Ala, Trp, Gly; and

Y is amide, thioether, thioester, disulfide, urea, carbamate, or sulfonamide.

25. (Withdrawn) The method according to claim 18 wherein the backbone cyclized somatostatin analog having the general Formula No. 8



Formula No. 8

wherein m and n are 1 to 5;

X designates a terminal carboxy acid, amide or alcohol group;

Y is amide, thioether, thioester, disulfide, urea, carbamate, or sulfonamide; and

the two cysteine residues are independently L or D.

26. (Withdrawn) The method according to claim 18 having the general Formula No. 5:

Z-Q-PTR

Formula No. 5

wherein

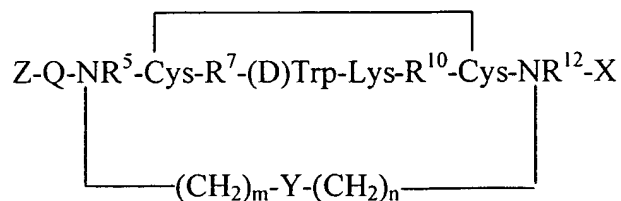
Z is a chelating moiety comprising: (i) four donor atoms selected from the group of N_3S and N_2S_2 that through metal complexation form three five- to six-membered rings or (ii) eight donor atoms that, through metal complexation, form stable five- to six-membered rings;

Q is a direct bond or a linker moiety which can be coupled to a free functional group of the peptide; and PTR denotes a backbone cyclized SST analog according to the present invention.

27. (Withdrawn) The method according to claim 26 wherein Q is selected from the group of a direct bond, diaminopropionic acid (Dpr), diaminobutyric acid (Dab), gamma aminobutyric acid (GABA), aminohexanoic acid, polyethylene glycol (PEG), 4-aminobutyric acid, 6-aminocaproic acid, and β -alanine, and Z is selected from the group of mercaptoacetyl-Gly-Gly-Gly (MAG3), 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) and diethylenetriaminepentaacetic acid (DTPA).

28. (Withdrawn) The method according to claim 27 wherein Z is selected from the group of mercaptoacetyl-Gly-Gly-Gly (MAG3), 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) and diethylenetriaminepentaacetic acid (DTPA); and Q is selected from a direct bond or Gly.

29. (Withdrawn) The method according to claim 26 wherein the backbone cyclized somatostatin analog having the general Formula No. 9



Formula No. 9

wherein m and n are 1 to 5;

X designates a terminal carboxy acid, amide or alcohol group;

Q is a direct bond or a linker moiety which can be coupled to any free functional group of the peptide;

Z is a chelating moiety comprising: (i) four donor atoms selected from the group of N_3S and N_2S_2 that through metal complexation form 5- to 6-membered rings or (ii) eight donor atoms that, through metal complexation, form stable five- to six-membered rings;

R^5 is (D)- or (L)-Phe or (D)- or (L)-Ala;

R^7 is (D)- or (L)-Trp, (D)- or (L)-Phe, (D)- or (L)-1Nal, or (D)- or (L)-2Nal, or (D)- or (L)-Tyr;

R^{10} is Thr, Gly, Abu, Ser, Cys, Val, (D)- or (L)-Ala, or (D)- or (L)-Phe;

R^{12} is (D)- or (L)-Phe or (D)- or (L)-Ala; and

Y is amide, thioether, thioester disulfide, urea, carbamate, or sulfonamide.

30. (Withdrawn) The method according to claim 29 wherein the backbone cyclized somatostatin analog is selected from the group of:

MAG3-PheC3**-Cys*-Phe-(D)Trp-Lys-The-Cys*-PheN3**-NH₂;

MA-Dap(MA)-Gly-Phe(C3**-Cys*-Phe-(D)Trp-Lys-Thr-Cys*-Phe(N3**-NH₂;

MA-Dap(Gly)-Gly-Phe(C3**-Cys*-Phe-(D)Trp-Lys-Thr-Cys*-Phe(N3**-NH₂;

Gly-Dap(MA)-Gly-Phe(C3**-Cys*-Phe-(D)Trp-Lys-Thr-Cys*-Phe(N3**-NH₂;

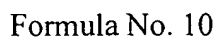
MA-Dap(MA)-GABA-Phe(C3**-Cys*-Phe-(D)Trp-Lys-Thr-Cys*-Phe(N3**-NH₂;

MA-Dap(Gly)-GABA-Phe(C3**-Cys*-Phe-(D)Trp-Lys-Thr-Cys*-Phe(N3**-NH₂;

Gly-Dap(MA)-GABA-Phe(C3**-Cys*-Phe-(D)Trp-Lys-Thr-Cys*-Phe(N3**-NH₂;

wherein MA denotes mercaptoacetyl, Dab denotes diaminobutyric acid, GABA denotes gamma aminobutyric acid, and one asterisk denotes that the two form a disulfide bridge, and two asterisks denotes that a second bridging group is connected between the N^{α} - ω -functionalized derivative of marked residues.

31. (Withdrawn) The method according to claim 26 wherein the backbone cyclized somatostatin analog having the general Formula No. 10



R¹² is Gly, Val, Leu, (D)- or (L)-Phe or 1Nal or 2Nal.

R⁹ is Lys;

R¹⁰ is Thr;
R¹¹ is Phe;
R¹² is Gly; and
n is 3.

33. (Withdrawn) The method according to claim 31 wherein the backbone cyclized somatostatin analog is selected from the group of:

In-DTPA-Gly-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
In-DTPA-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
In-DTPA-β-Ala-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
In-DTPA-GABA-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
In-DTPA-5-aminopentanoic acid-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
In-DTPA-3-aminomethylbenzoic acid-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-H₂;
ReO-MA-Dpr(MA)-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
ReO-MA-Dpr(MA)-Gly-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
ReO-MA-Dpr(MA)-βAla-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
ReO-MA-Dpr(MA)-GABA-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
ReO-MA-Dpr(MA)-5-aminopentanoic acid-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
ReO-MA-Dpr(MA)-6-aminohexanoic acid-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
ReO-MA-Gly-Gly-Gly-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
ReO-MA-Gly-Gly-Gly-Gly-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
ReO-MA-Gly-Gly-Gly-GABA-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;
ReO-MA-Gly-Gly-Gly-5-aminopentanoic acid-Dab*-Phe-Trp-(D)Trp-Lys-Thr-Phe-GlyC3*-NH₂;

wherein MA denotes mercaptoacetyl, Dpr denotes diaminopropionic acid, Dab denotes diaminobutyric acid, GABA denotes gamma aminobutyric acid, DTPA denotes diethylenetriaminepentaacetic acid, and the asterisk denotes that the bridging group is connected

between the free functional group of that residue and the N^α-ω-functionalized derivative of the Gly residue.

34. (Withdrawn)

35. (Withdrawn) The method according to claim [[34]] 18 wherein the radioisotope is selected from the group consisting of ^{99m}Tc, ¹⁸⁶Re, ¹⁸⁸Re, indium, yttrium, lutetium, gallium and gadolinium.

36. (Withdrawn) The method according to claim 18 wherein the backbone cyclic analog is selective for at least one somatostatin receptor subtype.

37. (Withdrawn) A method for diagnosing, treating or preventing of disorders selected from the group consisting of cancers, autoimmune diseases, endocrine disorders, diabetes-associated complications, gastrointestinal disorders, inflammatory diseases, pancreatitis, atherosclerosis, restenosis, allograft rejection, and post-surgical pain, comprising administering to a mammal in need thereof a pharmaceutical composition comprising a therapeutically effective amount of a backbone cyclized somatostatin analog according to claim 1, optionally with a pharmaceutically acceptable carrier.

38. (Withdrawn) The method according to claim 37 wherein the backbone cyclic analog is selective for at least one somatostatin receptor subtype.

39. (Previously Presented) A kit for preparing a scintigraphic imaging agent for imaging sites within a mammalian body, said kit comprising a backbone cyclized analog of somatostatin according to claim 1 and a chelating moiety covalently bound to said backbone cyclized analog.